

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

II. AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph at page 2, lines 1-12, with the following rewritten paragraph:

-- Muscarinic receptors are members of the G-protein coupled receptors that are composed of a family of five receptor sub-types (M_1 , M_2 , M_3 , M_4 and M_5) and are activated by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor subtypes in the brain and other organs has been documented (Bonner, T. I. et al., *Science* (Washington D.C.) **1987**, 237, 527-532; Goyal, R. K., *J. Med.*, **1989**, 321, 1022; Hulme, E.C., et al., *Annu. Rev. Pharmacol. Toxicol. Pharmacol. Toxicol.* **1990**, 30, 633; and Eglen, R. M. and Hegde, S. S., *Drug News Perspect.* **1997**, 10(8), 462-469). For example, the smooth muscle is composed largely of M_2 and M_3 receptors, cardiac muscle is composed largely of M_2 receptors, and salivary glands are largely composed of M_3 receptors. --

Please replace the paragraph at page 2, lines 13-21, with the following rewritten paragraph:

-- It has been established that the muscarinic receptors are involved in diseases such as chronic obstructive pulmonary disease, asthma, irritable bowel syndrome, urinary incontinence, rhinitis, spasmodic colitis, chronic cystitis, ~~cognitive~~ cognitive disorders (e.g. Alzheimer's disease), senile dementia, glaucoma, schizophrenia, gastroesophageal reflux disease, cardiac arrhythmia, blurred vision, and hyper salivation syndromes (Fisher, A., *Invest. Drugs*, **1997**, 6(10), 1395-1411; Martel, A. M., et al., *Drugs Future*, **1997**, 22(2), 135-137; Graul, A. and Castaner, J., *Drugs Future*, **1996**, 21(11), 1105-1108; and Graul, A., et al., *Drugs Future*, **1997**, 22(7), 733-737). --

Please replace the paragraph at page 3, lines 22-25, with the following rewritten paragraph:

-- R^x is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted

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alkynyl, acyl, acylamino, aminoacyloxy, aryl, carboxyalkyl, cycloalkyl,
 substituted cycloalkyl, cycloalkenyl, ~~substitutes~~ substituted cycloalkenyl,
 heteroaryl, heteroaralkyl, alkylsulfonyl, or alkylsulfinyl; --

Please replace the paragraph at page 10, line 24 to page 11, line 11, with the following rewritten paragraph:

-- The term "substituted alkyl" refers to an alkyl group as defined above wherein one or more carbon atoms in the alkyl chain have been optionally replaced with a heteroatom such as -O-, -S(O)_n- ~~-S(O)_n-~~ (where n is 0 to 2), -NR- (where R is hydrogen or alkyl) and having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, and -NR^aR^b, wherein R^a and R^b may be the same or different and are chosen from hydrogen, optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl and heterocyclic. This term is exemplified by groups such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-dimethylaminopropyl, 2-sulfonamidoethyl, 2-carboxyethyl, and the like. --

Please replace the paragraph at page 75, lines 6-9, with the following rewritten paragraph:

-- A ~~preferred~~ preferred value for X is alkylene optionally substituted with one, two, or three hydroxy groups, alkylene wherein one, two or three carbon atoms have been replaced by an oxygen atom, or an -alkylene-phenylene-alkylene- wherein the phenylene ring is optionally substituted with one or two chloro or fluoro groups. --

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Please replace the paragraph at page 75, lines 18-19, with the following rewritten paragraph:

-- Another preferred value for X is is nonane-1,9-diyl, octane-1,8-diyl, propane-1,3-diyl, 2-hydroxypropane-1,3-diyl, or 5-oxa-nonane-1,9-diyl. --

Please replace the paragraph at page 78, lines 12-22, with the following rewritten paragraph:

-- A preferred group of compounds are compounds of formula (I) wherein L₂ is a group of formula (d) wherein R⁴⁶ is alkyl that is optionally substituted with from 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, NR^aR^b, wherein R^a and R^b may be the same or different and are chosen from hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and heterocyclic. --

Please replace the paragraph at page 85, lines 4-8, with the following rewritten paragraph:

-- Suitable dihydroxyl and dihalo starting materials useful for incorporating a group X into a compound of the invention are shown in the following table. Preferably, an alcohol is reacted with a ligand bearing a leaving group to provide an ether bond, while a dihalo compound is preferably reacted with an amine of the ligand to form a ~~substituted~~ substituted amine.

Please replace the paragraph at page 97, line 30 to page 98, line 3, with the following rewritten paragraph:

-- Compounds of formula (I) can conveniently be prepared using combinatorial

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synthesis methods (e.g. solid phase and solution phase combinatorial synthesis methods) that are known in the art. For example, compounds of formula (I) can be prepared using combinatorial methods like those ~~escribed~~ described in International Patent Application Publication Number WO 99/64043. --

Please replace the paragraph at page 118, line 26 to page 119, line 4, with the following rewritten paragraph:

-- For data analysis, the oxotremorine response (zero inhibition) was determined by measuring the mean pressure 1 minute prior to the antagonist injection. Then, to assess antagonist inhibition, mean pressure was ~~mesured~~ measured beginning at 1 minute and ending 2 minutes after antagonist administration. If the pressure had not leveled off after 1 minute, a wait was initiated until it was stable and then a 1-minute sample of the mean was taken. Lastly, to determine the true 100% inhibition point, the mean pressure was measured beginning 1 minutes and ending 2 minutes after the high dose atropine challenge. The percent inhibition by the antagonist can be determined by the ratio of the decrease from the zero to 100% values. --